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EXAMINER	
HINES, JANA A	
ART UNIT	**PAPER NUMBER**
1645	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/23/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/676,005	ANDERSON, NORMAN L.	
	Examiner	Art Unit	
	Ja-Na Hines	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 July 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *44-72* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *44-72* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/26/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

SUPPLEMENTAL DETAILED ACTION

Office Action Vacated

1. Applicant's request for vacating the last Office Action is persuasive and therefore, the action dated October 23, 2006 is withdrawn.

Amendment Entry

2. The amendment July 10, 2006 has been entered. The examiner acknowledges the amendment to the specification. Claims 1-43 have been cancelled. Claims 44-72 have been newly added. Claims 44-72 are under consideration in this office action.

Withdrawal of Rejections

3. The following objections and rejections have been withdrawn in view of applicants' amendments and arguments:

a) The objection of claims 2 and 38;
b) The written description rejection of claims 1-26 and 37-41 under 35 U.S.C. 112, first paragraph;
c) The rejection of claims 1-26 and 37-41 under 35 U.S.C. 112, second paragraph;
d) The rejection of claims 1-5, 11-15, 19-20 and 37-41 under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Geng et al;
e) The rejection of claims 6-8 and 10 under 35 U.S.C. 103(a) as being unpatentable over Geng et al., and Niederkofler et al; and
f) The rejection of claims 16-21 under 35 U.S.C. 103(a) as being unpatentable over Geng et al., and Wall et al.

Response to Arguments

4. Applicant's arguments filed July 10, 2006 have been fully considered but they are not persuasive. Applicant's arguments with respect to claim 1-26 and 37-41 have been considered but are moot in view of the new ground(s) of rejection.

New Grounds of Rejection

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 44-47, 52-60, 67 and 71-72 are rejected under 35 U.S.C. 102(b) as anticipated by Geng et al. (J. of Chromatography A, 2000, Vol. 870: page 295-313).

The claims are drawn to a method of quantifying the amount of at least a first protein and a second protein in a biological sample, the first protein having a first monitor peptide and the second protein having a second monitor peptide, the first monitor peptide and the second monitor peptide being produced by digestion of the first protein and the second protein, respectively, by a proteolytic agent, comprising: exposing the first monitor peptide and a labeled version of the first monitor peptide to a first binding agent, the first monitor peptide bound to the first binding agent and the labeled version of the first monitor peptide bound to the first binding agent being first bound peptides; exposing the second monitor peptides and a labeled version of the

second monitor peptide to a second binding agent, the second binding agent being different from the first binding agent, the second monitor peptide bound to the second binding agent and the labeled version of the second monitor peptide bound to the second binding agent being second bound peptides; peptides produced by the digestion of the first protein and the second protein not bound to the first binding agent or the second binding agent being unbound peptides, separating at least some of the bound peptides from at least some of the unbound peptides; and measuring the amount of the first monitor peptide that was separated from at least some of the unbound peptides using a mass spectrometer.

Geng et al., teach signature peptide approaches to detecting proteins in complex mixtures. Proteins in complex mixtures were digested to create classes of peptide fragments (abstract). Several purification techniques were disclosed, including serial lectin affinity columns, anion-exchange chromatography, metal affinity chromatography or capillary electrophoresis as being used to separate the fractionated peptides (page 299). The sample was digested (page 298), just as required by the claims. Classes of peptide fragments were selected by affinity chromatography using different lectin columns (abstract). The digested samples were injected onto the column (page 298). The digested human serotransferrin was injected onto a ConA affinity column (page 296). Thus a first binding agent in the form of ConA was taught, just as required by the claims. Affinity selection was also performed using the *Banderaea simplicifolia* (BS-II) lectin affinity columns (page 298). Thus the second binding agent, different from the first binding agent is taught. The column or support is a packed column, having a lectin as

the binding agents just as required by the claims. The analytes displaced from the column were then eluted (page 298). Geng et al., teach silica based columns, thereby teaching monolithic porous beads as the support (pages 298 and 300). Geng et al., teach sequential loading and elution of the products (page 298). Also taught is a wash of the column, which removed unbound analyte (page 298). Figure 4(b) shows two glycopeptides isolated from a ConA column. Thereby teaching at least two monitor peptides, just as required by the claims. The eluted peptides were monitored and fractions were collected for MALDI-time of flight mass spectrometry analysis (MALDI-TOF-MS) (page 298). The equations were deduced from the ratios of deuterium-labeled and unlabeled acetylated peptides (page 299). Figure 7 shows signature peptides having masses at different peaks, thus there are clearly multiple peptides in the mixture. Figures 5 and 7 show mass spectrum results from a first and second glycopeptides, thereby teaching a first and second protein, just as required by the claims.

Geng et al., teach the synthesis of *N*-acetoxysuccinamide, *N*-acetoxysuccinamide and d_3-C^1 N-acetoxysuccinamide as different isotopic labels added to the peptides (page 298). Thus the art teaches that the introduction of labeled versions of the monitor peptide having stable isotopes, just as required by the claims. Furthermore the art teaches at least two differently labeled peptides being prepared and loaded onto the support system and mass spectrometer, just as required by the claims. The MALDI-TOF-MS was performed using a mass spectrometer (page 298), just as required by the claims. The data teaches that proteins may be quantified as signature

peptides using isotopically labeled internal standards (abstract) or monitor peptides. This is based on the concept of using and adding the mixture a very similar, but distinguishable substances and determining the concentration of analyte relative to a known concentration of the internal standard (page 308). The signature peptides and monitor peptides are all generated by trypsin digestion (page 308). Figure 9(a) depicts the mass spectrum of the labeled and unlabeled peptide. Thus a first peptide and labeled monitor peptide are clearly taught. Isotopes ratios of peptides were determined by MALDI-MS and used to determine the concentration of a peptide relative to that of the labeled internal standard peptides (abstract).

Geng et al., also a method for quantifying the amount of a target protein in a biological sample as recited by claim 67. The proteins in complex mixtures were digested with a proteolytic agent to create classes of peptide fragments, just as required by the claim. The digested samples thereby creating a mixture were injected onto the affinity column (page 298). Thus a binding agent in the form of ConA was taught, just as required by the claims. Figure 4(b) shows glycopeptides isolated from a ConA column, Thereby teaching monitor peptides, just as required by the claims. The mixture and separation by elution meets the instantly recited separation step. The eluted peptides were monitored and fractions were collected for MALDI-time of flight mass spectrometry analysis (page 298). The equations were deduced from the ratios of deuterium-labeled and unlabeled acetylated peptides (page 299). Geng et al., teach measuring the amount of the monitor peptides using a mass spectrometer, just as required by the claims.

Thus Geng et al., teach all the steps of the instantly claimed methods of quantification including the different supports, along with the use of labeled stable isotopes.

Response to Arguments

5. Applicant's arguments filed July 10, 2006 have been fully considered but they are not persuasive. Applicants urge that the new claims "exposing the first monitor peptide and a labeled version of the first monitor peptide to a first binding agent.., exposing the second monitor peptide and a labeled version of the second monitor peptide to a second binding agent, the second binding agent being different than the first binding agent and that none of Geng, Niederkofler, and Wall, alone or in proper combination, discloses such a method. However, Geng et al., disclose the use of at least two peptides, as shown by the mass spectrums depicting at least two peptides. Figure 7 shows signature peptides having masses at different peaks, thus there are clearly multiple peptides in the mixture. Geng et al., also teach the use of at least two monitor peptides, contrary to applicants' assertions.

6. Claims 48-49, 61, 62-66 and 68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Geng et al., (J. of Chromatography A, 2000, Vol. 870: page 295-313) in view of Zhao et al. (PNAS. 1996. Vol. 93:4020-4024).

The claims are drawn to a method for quantifying the amount of at least a first protein and second protein in a biological sample drawn to antibodies as binding

agents. Geng et al., have been discussed above, however Geng et al., do not teach the use of antibodies as binding agents.

Zhao et al., teach mapping protein-protein interaction by affinity-directed mass spectrometry. Figure 1 shows the strategy for defining binding sites in a protein that interacts specifically with monoclonal antibody (mAb). Step I shows proteolytic digestion; Step II shows immunoprecipitation wherein the antibody aids in the immunoprecipated complex wherein the unbound peptides are washed away; and Step III shows matrix-assisted laser desorption mass spectrometric analysis. The monoclonal antibody was prepared against human growth fibroblast growth factor (page 4020). The antibody and the mixture of peptides produced by the proteolytic digestion were mixed and the mixture was applied the protein G/protein A agarose bead column (page 4021). The Materials and Methods teach mass spectrometry analysis (page 4021).

Therefore, it would have been prima facie obvious at the time of applicants invention to modify the method for quantifying the amount of at least two proteins in a biological sample as taught by Geng et al., wherein the modification uses antibody binding agents as taught by Zhao et al. One would have a reasonable expectation of success in incorporating other binding agents, such as antibodies into the method since no more than routine skill would have been required to exchange the binding agents of Geng et al., for those of Zhao et al., since Geng et al., teach that affinity purification is useful in such methods. Furthermore, only routine skill is required since both Geng et al., and Zhao et al., both teach methods for quantifying the amount of at least two proteins in a sample by means of a digestion step, an exposure and binding step, a

wash and elution step and measurement step, just as instantly claimed. Thus one having ordinary skill in the art would have been motivated to make such a change since only the expected results would have been obtained, like increased specificity in binding due to using antibodies. Therefore the use of a known member of a class of binding agent materials is not patentable if other members of the class of binding agent materials were known to be useful for that same purpose.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 44-72 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a) The preamble of the claim 44 is drawn to a method of quantifying the amount of at least a first protein and a second protein in a biological sample, however the final step of the method refers to measuring the amount of the first monitor peptide. There is no correlation step which correlates the measuring the amount of the first monitor peptide and quantifying the amount of at least a first protein and a second protein. Therefore, the goal of the preamble is not commensurate with the steps of the method that are drawn to quantifying proteins. Similarly, claims 61 and 67 are unclear for the same reason.

b) Claims 44, 61 and 67 refer to exposing the monitor peptide and a labeled version of the monitor peptide to a binding agent, wherein the monitor peptide bind to the binding agent and the labeled version of the monitor peptide bind to the binding agent. However it is unclear if a single binding agent binds both the unlabeled and labeled peptide or the binding agent binds either the labeled or unlabeled peptide. It is also unclear what the phrase "the labeled version of the second monitor peptide bound to the first or second binding agent being first or second bound peptide" comprises. The make-up of the first and second bound peptides is unclear. Thus, clarification is required to overcome the rejection.

c) The phrase "at least some of the bound peptides from at least some of the unbound peptides " in claims 44, 45, 46, 61 and 67 is a relative phrase which renders the claim indefinite. The phrase is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Thus the metes and bounds of the term cannot be ascertained. It is unclear how to define the at least some. Thus, clarification is required to overcome the rejection.

d) Claim 67 recites the limitation "the mixture " in the claim. There is insufficient antecedent basis for this limitation in the claim.

e) Claims 68-70 recite the limitation "the first binding agent" in the claims. There is insufficient antecedent basis for this limitation in the claim.

f) Claim 66 is unclear. It is unclear how the selection of a monitor peptide is not inherently accomplished by independent claim 61. If the target protein includes the

monitor peptides, then hasn't the monitor peptide already been selected? Similarly, if claim 61 uses an antibody, then it would appear that the antibody has already been created. Thus, clarification is required to overcome the rejection.

Prior Art

8. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Geng et al. (J. of Chromatography B, 2001, Vol. 752: page 293-306). Riggs et al., (J. of Chromatography A, 2001, Vol. 924: page 359-368). Suckau et al., (PNAS, 1990, Vol. 87:pages 9848-9852).

Conclusion

9. No claims allowed.

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is 571-272-0859. The examiner can normally be reached on Monday-Thursday and alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Jeffery Siew, can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Ja-Na Hines
January 25, 2007

MARK NAVARRO
PRIMARY EXAMINER